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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,743	03/14/2001	Peter L. Pedersen	JHU1720-1	4365

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Lisa A. Haile, J.D., Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER

MCGARRY, SEAN

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/808,743

Applicant(s)

PEDERSEN ET AL.

Examiner

Sean R McGarry

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 27-33 is/are pending in the application.
- 4a) Of the above claim(s) 4, 5, 17, 18, 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6-16, 27, 28 and 30-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-3, 6-16 remain rejected and new claims 27, 28, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of growth of AS-30D hepatoma cell line in culture via the expression of SEQ ID 1 in antisense orientation, does not reasonably provide enablement for the full scope instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This rejection is maintained for the same reasons of record set forth in the Official Action mailed 7/25/03.

The instantly claimed invention is drawn to the inhibition of tumor cell in culture or in a whole animal via the inhibition of a hexokinase a targeted antisense transcript or oligonucleotide (claims 1 and 6-16). The elected invention is drawn to inhibition via antisense targeted to a type II hexokinase including SEQ ID NO: 1. The instant invention reads on antisense-based therapy of cancer. These cancers include tumors in tissues of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hemotopoietic, breast, thymus, testis, ovary, and uterus. The invention also includes the treatment of cancers such as low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, hepatoma, colorectal cancer, colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, endometrial cancer, bone cancer, squamous cell cancer and neuroblastoma. The breadth of cancers contemplated for treatment is indeed vast.

The instant specification shows the inhibition of AS-30D hepatoma cells in culture upon their transfection with an antisense Type II hexokinase (SEQ ID NO:1) expression vector. It has been shown that expression of SEQ ID NO: 1 in antisense orientation can inhibit AS-30D cell growth. The specification fails to show how the inhibition of a Type II hexokinase that may also inhibit both a Type I and Type II hexokinase in one cell line correlates to the inhibition of tumor cell growth via the inhibition of any one particular hexokinase in other cells and further in cell of a whole animal. The instant specification indicates that it is "highly likely" that both a Type I and a Type II hexokinase are inhibited by an antisense transcript of SEQ ID NO: 1 (see page 40). The specification therefore fails to demonstrate the inhibition of cell grow is due to the inhibition of either a Type I or Type II hexokinase alone.

Applicants priority document indicates that it is only Type II and to a lesser extent Type I that are over expressed in highly glycolytic tumors. It is further indicated that the experiments, which parallel those of the instant specification were designed to inhibit both Type I and Type II hexokinase (see page 3 of the priority document, for example). The instant specification has failed to show a correlation that hexokinase overexpression, for example, is causative of the broad range of cancers instantly considered for treatment.

Newgard et al (US 5,891,717) states at column 17 "[h]owever, the correlation [increases in low Km hexokinase activity correlation with cell transformation] has not been proven to exist as a cause and effect relationship." This would indicate that one in the art would be required to determine the relationship of any particular hexokinase with

any particular cancer to determine its suitability as a target for the treatment of a vast array of cancers, for example.

Furthermore the art of antisense-based therapy is in general an unpredictable art where the instant specification provides no specific guidance for the treatment of any specific cancer by targeting any particular hexokinase, for example. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: “[a]ntisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven.”; “[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest.”; “[h]owever, their unpredictability confounds research applications of nucleic acid reagents.”; “[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.”; “Years of investigation can be required to figure out what an ‘antisense’ molecule is actually doing. . . .”; “Because knowledge of their underlying mechanism is typically lacking, non-antisense effects muddy the waters.”; “because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all

pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known.”; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range.”; “[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells.”; “[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible.”; and, “[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*.”

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert “[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive.” It is also stated “[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment

approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: "[t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . . [i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

The instant specification fails to provide any particular target for any particular disease and further has not provided any specific guidance on how to make an antisense that would be predictably effective for treating any of the vast array of diseases instantly contemplated. One in the art would be left to determine all of these determinations by engaging in undue trial and error experimentation, for example.

Applicant's arguments filed 6/25/04 have been fully considered but they are not persuasive.

Applicant argues that the examiner appears to be importing or reading limitations into the claims. The interpretation of the claims is not unreasonable based on the disclosure of the instant application. Nothing asserted in the Official Actions of record is inconsistent with the disclosure of applicants specification. The claims are broad. Those embodiments that may not be expressly recited in the claims are not therefore excluded. It is the examiners responsibility to give the claims their broadest reasonable interpretation. If applicant believes that those embodiments addressed in the rejections of record are inconsistent with the claims in light of the specification, applicant is invited to point out why the interpretation is not reasonable. Applicant argues that the examiner reliance on Newgard et al is not reasonable since other compounds have been used to treat cancer where the compound affect cells other than cancer cells. The argument does not provide any evidence that one in the art would not need to engage in undue experimentation with this factor in addition to the numerous other points made for the unpredictable state of the antisense art. Applicant has not shown how this assertion

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shows that the claimed invention would function as the asserted "other compounds".

Each factor considered for enablement is not in a vacuum but the many considerations are taken as a whole and, as asserted in the rejection of record, those considerations for the claimed invention clearly show that there are many obstacles such as that relied upon in Newgard et al and for the many other reasons set forth in the rejection of record for non-enablement. Applicant asserts that since they have shown inhibition in one cell type one in the art would make the assumption that the cell growth inhibition observed in that cell type would follow for all other cells. Newgard et al (US 5,891,717) states at column 17 "[h]owever, the correlation [increases in low K_m hexokinase activity correlation with cell transformation] has not been proven to exist as a cause and effect relationship." This would indicate that one in the art would be required to determine the relationship of any particular hexokinase with any particular cancer to determine its suitability as a target for the treatment of a vast array of cancers, for example. The state of the art of nucleic acid based therapies and the references relied upon for this unpredictability show that, at least for treating a particular disease where the range of potential conditions contemplated by applicant, which is indeed vast and not clearly defined, requires adequate guidance.

Applicant argues that there is no basis for the Actions assertion that a correlation has not been established for the inhibition of Type I and Type II hexokinase vs. inhibition of Type I or Type II. Applicant is again directed to their priority document that clearly indicates that the methods used in the instant specification were specifically designed to inhibit both Type I and Type II hexokinase. There has been no showing of

the inhibition of only Type I or Type II in the instant specification and the Exhibits provided by applicant do not show the correlation either. Applicant argues that one in the art would know, based on the homology of Type I and Type II hexokinases, that an antisense molecule based on either hexokinase [Type I or Type II] likely would inhibit the activity of both. It is noted that this cross inhibition is not necessarily true for all antisense and further is not required by the claims. Applicant has argued that the claims do not specifically recite that both or either or of the Type I or Type II hexokinases are inhibited and therefore is not an issue of enablement. The specification clearly discusses this and the claims clearly embrace the embodiments addressed and therefore are a factor in the determination of enablement. The rejection of record is maintained for the reasons of record. It is noted that applicants argument do not address the state of the art as evidenced by the references cited by the examiner.

Claims 1-3, 6-16, 27, 28, and 30-33 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 1, which corresponds to the cDNA of the human species of Type II hexokinase. The claimed invention is drawn to the inhibition of a Type II hexokinase via antisense in a method of treating a vast range of cancers. The claims are so broad as to embrace encompass the inhibition corresponding sequences

from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth and the treatment of any cancer that may have a "highly glycolytic phenotype". The methods require the use of antisense oligonucleotides which structures have not been disclosed. The specification does not disclose the sequence (ie structure) of any other antisense molecule other than the full expressed SEQ ID NO: 1 in antisense orientation. The specification fails to first describe the structure of the vast range of possible targets and second fails to provide the structure of antisense molecules that have a structure that has been shown by the specification of the art to correlate with the function of inhibiting tumor cell growth. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Although the specification may provide a method to find potential antisense inhibitors, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird,

30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* ,

984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant where, for example there has been no establishment of a structure known in the art or shown by the specification to correlate with the specific function of inhibiting a hexokinase such that a tumor cell is inhibited, especially in the context of treating a disease. Applicant is reminded that Vas-Cath makes clear that the

written description provision of 35 USC 112 is severable from its enablement provision.
(See page 1115.)

The species exemplified in the application, for example, inhibits both Type I and Type II hexokinase, while the scope of the instant invention embraces the inhibition of only a Type II hexokinase. There have been no such species described in the instant application.

Applicant's arguments filed 6/24/04 have been fully considered but they are not persuasive.

Applicant argues the written description rejection by again asserting that the examiner is reading limitations into the claims. If applicant believes that the embodiments addressed in the rejection of record are not embraced within the scope of the claimed invention they should provide reasons why these embodiments would not be reasonably interpreted to be included in the scope of the claimed invention.

Applicant points to page 13, lines 20-21 of the specification for support of the description of the claimed invention. It appears that that description is limited to preferred embodiments and further does not provide a description such that one would know the structure of the compounds required to perform the claimed methods. It appears that applicants' specification provides the description of one antisense polynucleotide and then a method to find others. As was asserted in the rejection of record; Although the specification may provide a potential method to find antisense

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inhibitors, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. It appears that a method to find a compound is not a substitute for the description of or the compound itself. Applicant offers two exhibits as evidence for an adequate written description. It is noted that the determination of antisense molecules for use in a method as claimed requires more than just a knowledge of the target sequence. The determination of an effective antisense also depends on the sequence and secondary structure of the targeted nucleic acid. There is no disclosed structure in the instant application or in the prior art for what provides the function of inhibition for antisense in general or a structure such that one would know a hexokinase Type II would specifically be inhibited by a particular antisense oligonucleotide. Each antisense compound must be determined empirically. If there exist methods that help one in their empirical search that is great, but it does not provide one with a description of the structure of any particular antisense compound. It is noted that in the Exhibit, Lehman et al., it is stated that their method of theoretical design does not even work for antisense compounds of 100 nucleotides. The compound for use in the claimed method have not been described in a manner that one in the art would know the structure of any particular compound that would have the ability to inhibit a particular hexokinase Type II). The targeted hexokinase (Type II) are not necessarily even limited to a particular sequence but reads on any hexokinase from any organism and may be any allele thereof, for example. Applicant is also directed to

University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004) where it was decided that a method that uses a compound described only by its function and a potential method to find such compounds does not satisfy the written description requirement.

The mere description of a polynucleotide that is complementary to a targeted sequence is not sufficient for the description of an antisense oligonucleotide that inhibits the expression of the target since there is more to the structure function relationship of antisense to a target than mere complementarity and that structure is not shared between any particular antisense compounds, for example. This is even more complicated by the methods requiring a treatment of disease since as asserted by the reference in the enablement rejection above, antisense shown to inhibit in cell in culture do not necessarily inhibit in an in vivo environment.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

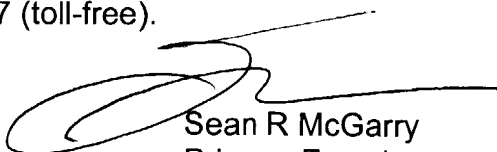
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sean R McGarry
Primary Examiner
Art Unit 1635

SRM